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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/911,610	07/25/2001	Shui-on Leung	018733-1053	3464

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 03/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/911,610	LEUNG, SHUI-ON	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-12 and 15-43* is/are pending in the application.

4a) Of the above claim(s) *21-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-12,15-20,42 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claim 1 has been canceled.

Claims 2, 5, 9-11, 15-19 been amended.

Claims 42 and 43 have been added.

2. Claims 21-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions. Applicant timely traversed the restriction (election) requirement in Paper No. 13.

3. Claims 2-12, 15-20, 42-43 are under examination.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

5. The following Office Action contains NEW GROUNDS of rejections.

Specification

6. The disclosure is still objected to because of the following informalities and were not addressed in the response filed 11/8/04:

The amendment filed 2/27/04 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The amendment updated the first line of the specification to add that "the contents of which are hereby incorporated by reference in their entirety".

Applicants are directed to the following:

United States Patent and Trademark Office OG Notices:
1268 OG 89 (18 March 2003).

Last paragraph of OG notice reads:
Part VII: Adding an Incorporation-By-Reference Statement in a Benefit Claim is Not Permitted After Filing An incorporation-by-reference statement added after the filing date of an application is not permitted because no new matter can be added to an application after its filing date. See 35 U.S.C. 132(a). If an incorporation-by-reference statement is included in an amendment to the specification to add a benefit claim after the filing date of the application, the amendment would not be proper. When a benefit claim is submitted after the filing of an application, the reference to the prior application cannot include an incorporation-by-reference statement of the prior application. See Dart Industries v. Banner, 636 F.2d 684, 207 USPQ 273 (C.A.D.C. 1980). Therefore, the Office will not grant a petition to accept a benefit claim that includes an incorporation-by-reference statement of a prior application, unless the incorporation-by-reference statement was submitted on filing of the application.

Applicant is required to cancel the new matter in the reply to this Office Action.

Rejections Withdrawn

7. The rejection of claims 5, 7, 8 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

8. The rejection of claims 5, 7, and 8 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendments to the claims.

9. The rejection of claims 1-12, 15-20 under 35 U.S.C. 103(a) as being unpatentable over Schoonjans et al (WO 99/37791, published 7/29/99, IDS #10), and further in view of Hansen et al (U.S. Patent 5,635,603, issued 6/97) and Lindhofer et al

(U.S Publication US20002/0051780, filed 9/97) is withdrawn in view of the amendments to the claims.

10. The rejection of claims 1-2, 9-10, 11-18 under 35 U.S.C. 103(a) as being unpatentable over Harris et al (WO 94/09131, published 4/94, IDS #10), and further in view of Chaudhary et al PNAS 87:1066-70, 1990) and Hansen et al (U.S. Patent 5,635,603, issued 6/97) is withdrawn in view of the amendments to the claims.

The following are NEW GROUNDS of rejections/Response to Arguments

Claim Rejections - 35 USC § 112

11. Claims 2-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 2, 5-6 recites the limitation "said first immunoglobulin-like domain" and "said second immunoglobulin-like domain" in claims 42 or 43 (or 2, 3, 5). There is insufficient antecedent basis for this limitation in the claims.

12. Claims 43, 2-12, 15-20 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line which produces an antibody having the exact chemical identity of mAb 734 and mAb hMN14 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different VH chains (about 50% homologous) can combine with the same VK chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different VH sequences combine with different VK sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species mAb 734 and mAb hMN14. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

13. Claims 42, 43, 2-12, 15-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schoonjans et al (WO 99/37791, published 7/29/99, IDS #10), and further in view of Hansen et al (US Patent 5,635,603, filed 12/94) and Lindhofer et al (U.S Publication US20002/0051780, filed 9/97) and Qu et al (Journal of Immunological Methods 213:131-144, 1998) and Hansen et al US Patent 5,874,540, filed 10/94) and Gautherot et al (J. Nucl Med. 39:1937-43, 1998) as evidenced by the specification.

The claims recite a target binding protein comprising a first polypeptide comprising a light chain of a Fab fused to a scFv and a second polypeptide comprising a heavy chain of a Fab fused to a second scFv wherein the scFv form two binding sites and the heavy and light chain domains associate to form a third binding site and wherein one binding site binds tumor marker and one binds hapten and wherein at least one of the heavy or light chains comprise a constant region glycosylation site and a carbohydrate is linked to the glycosylation recognition site. Further claimed is wherein one binding site is from mAb hMN14 and one from mAb 734 and wherein the scfv and immunoglobulin-like domains are linked by a constant region associates with a disulfide bond and the domains are linked by a linker and wherein at least two of the three domain binding sites have different binding or the same specificity, and further the polypeptide comprises a peptide tag, a cytokine, wherein the target is a tumor antigen and surface protein of T cells, wherein the linker is SEQ ID NO:1 and SEQ ID NO:2 and wherein the first polypeptide or second polypeptide has a N-glycosylation site with a carbohydrate and a conjugate to the carbohydrate is a toxin and the molecules bind CD28 and CD3.

Schoonjans et al teach scFv molecules conjugated through a CL or CH1 by a linker to a VH or VL and a second polypeptide comprising a scFv and a CL or CH1 and a VL or VH (see entire document, especially Figures 7A, 9A) and the molecules can bind two of the same antigens (Figure 9A) or different antigens (figure 7A) and the molecules have a disulfide bond in the extra amino acid sequence which is the constant region (see figures) and the molecules can have a tag or cytokine or other molecules attached to the binding sites (see page7). Schoonjans et al also teach the molecules bind CD3. Schoonjans et al does not teach a N-glycosylation site in the constant region or a toxin linked to the carbohydrate site or that the molecules bind CD28 and CD3 or the linkers of SEQ ID NO:1 and 2 and the mAb hMN14 and mAb 734.. These deficiencies are made up for in the teachings of Hansen et al, Lindhofer et al, Qu et al, Hansen et al and Gautherot et al.

Hansen et al teach adding a carbohydrate recognition site to antibodies for conjugation and the antibody can be a single chain FV (see column 6, lines 30-34) and conjugation to toxins or labels for therapy and the labels can be DPTA (see entire document).

Lindhofer et al teach bispecific and trispecific antibodies wherein the molecule binds a tumor antigen and CD3 and CD28 (see page 1).

Qu et al teach adding a carbohydrate recognition site in the antibody fragment in the CH1 domain and conjugates to the carbohydrate moiety for site specific conjugation for therapy (see entire document).

Hansen et al teach the hMN14 antibody which binds CEA and therapy methods.

Gautherot et al teach bispecific antibodies of anti-CEA and anti-DPTA.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a molecule comprising three binding sites as taught by Schoonjans et al and add a glycosylation site in the constant domain as taught by Qu et al and conjugate a toxin to the site as taught by Hansen et al and bind the antigens of CD3 and CD28 as taught by Lindhofer et al and one site for hMN14 and one of mAb 734.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a molecule comprising three binding sites as taught by Schoonjans et al and add a glycosylation site as taught by Qu et al and conjugate a toxin to the site as taught by Hansen et al and bind the antigens of CD3 and CD28 as taught by Lindhofer et al and one site for hMN14 and one of mAb 734 because Hansen et al teach engineered antibodies which can be scFv with added glycosylation sites and conjugation to toxins and other molecules such as DTPA for therapeutic and the method does not alter antigen binding and the molecules are used for therapeutics. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a molecule comprising three binding sites as taught by Schoonjans et al and add a glycosylation site as taught by Qu et al and conjugate a toxin to the site as taught by Hansen et al and bind the antigens of CD3 and CD28 as taught by Lindhofer et al and one site for hMN14 and one of mAb 734 because Lindhofer et al teach trispecific molecules for targeting tumors and T cells and the molecules are directed to killing tumor cells (see

page 5). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a molecule comprising three binding sites as taught by Schoonjans et al and add a glycosylation site as taught by Qu et al and conjugate a toxin to the site as taught by Hansen et al and bind the antigens of CD3 and CD28 as taught by Lindhofer et al and one site for hMN14 and one of mAb 734 because Schoonjans et al teach trispecific molecules binding to CD3 and tumor antigens and conjugation of other molecules such as toxins and cytokines for treatment of diseases. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a molecule comprising three binding sites as taught by Schoonjans et al and add a glycosylation site as taught by Qu et al and conjugate a toxin to the site as taught by Hansen et al and bind the antigens of CD3 and CD28 as taught by Lindhofer et al and one site for hMN14 and one of mAb 734 because Qu et al teach adding a carbohydrate recognition site to the CH1 domain and conjugation of molecules for therapy and the CH1 domain mutants were preferred for conjugation of larger molecules for therapy and the grafting of the CH1-appended sites to other antibodies only involves simple V-region replacement (see page 144). In addition one would have used the binding site of the hMN14 and 734 antibodies because as evidenced from the specification the term "734" means an antibody that binds DTPA (see page 36) and as taught by Hansen the hMN14 binds CEA and as taught by Gautherot et al a bispecific antibody of anti-CEA and anti-DTPA was used to target tumors and treat tumors with radiolabels. Because claim 43 only recites an antibody by laboratory definition the art reads on the claim for an anti-DTPA

antibody "734". It would have been obvious to label the molecules with the method of Hansen et al or Qu et al because of the advantages disclosed of not altering the antigen binding or specificity and it would have been obvious to use the claimed linkers because any linker would satisfy the requirement of separating the domains.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The response filed 11/8/04 has been carefully considured but is deemed not to be persuasive. The response states that there is no teachings in Schoonjans for a N-glycosylation site in the constant region and Hansen does not teach adding the site anywhere else. In response to this argument, the new rejection addresses this by referring to Qu et al for adding a constant region site and conjugation and Hansen provides motivation and reasonable expectation of success to add toxins and other molecules to the added carbohydrate site.

14. Claims 42, 43, 2-3, 5-12, 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris et al (WO 94/09131, published 4/94, IDS #10), and further in view of Chaudhary et al PNAS 87:1066-70, 1990) and Hansen et al (U.S. Patent 5,635,603, issued 6/97) and Qu et al (J. of Immunological Methods 213:131-144, 1998) and Hansen et al US Patent 5,874,540, filed 10/94) and Gautherot et al (J. Nucl Med. 39:1937-43, 1998) as evidenced by the specification.

The claims have been described supra.

Harris et al teach a polypeptide comprising a scFv with a VL-CL and a polypeptide with a scFv and a VH-CH1 (see Figure 8) and the molecules can be trivalent and association domains of VL and VH and the scFv sites can be the same or different and the third site can be different from the two other sites (see page 26). Harris et al does not teach a conjugate or a glycosylation site in the constant region for conjugation to toxins or binding to toxin and tumor antigens and mAb hMN14 and mAb 734. Theses deficiencies are made up for in the teachings of Chaudhary et al, Hansen et al, Qu et al, Hansen et al, and Gautherot et al.

Hansen et al teach adding a carbohydrate recognition site in the antibody fragment and the antibody can be a single chain FV (see column 6, lines 30-34) and conjugation to toxins or labels for therapy (see entire document).

Chaudhary et al teach fusion protein at the C terminus to scFv for therapy.

Qu et al teach adding a carbohydrate recognition site in the antibody fragment in the CH1 domain and conjugates to the carbohydrate moiety for site specific conjugation for therapy (see entire document).

Hansen et al teach the hMN14 antibody which binds CEA and therapy methods.

Gautherot et al teach bispecific antibodies of anti-CEA and anti-DPTA.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a molecule comprising three binding sites as taught by Harris et al and add a glycosylation site as taught by Qu et al

and conjugate a toxin to the site as taught by Hansen et al or add a polypeptide to the C-terminus as taught by Chaudhary et al and one site for hMN14 and one of mAb 734 .

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a molecule comprising three binding sites as taught by Harris et al and add a glycosylation site as taught by Qu et al and conjugate a toxin to the site as taught by Hansen et al add a polypeptide to the C-terminus as taught by Chaudhary et al and one site for hMN14 and one of mAb 734 because Hansen et al teach engineered antibodies which can be scFv with added glycosylation sites for conjugation to toxins and other molecules for therapeutic and the method does not alter antigen binding and the molecules are used for therapeutics. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a molecule comprising three binding sites as taught by Harris et al and add a glycosylation site as taught by Qu et al and conjugate a toxin to the site as taught by Hansen et al or add a polypeptide to the C-terminus as taught by Chaudhary et al and one site for hMN14 and one of mAb 734 because Chaudhary et al teach adding a toxin to the C-terminus for therapeutic reasons to target tumor cells. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a molecule comprising three binding sites as taught by Harris et al and add a glycosylation site as taught by Qu et al and conjugate a toxin to the site as taught by Hansen et al or add a polypeptide to the C-terminus as taught by Chaudhary et al and one site for hMN14 and one of mAb 734 because Harris et al teach the molecules are used for therapeutics and

can bind toxins or cells (see page 4). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a molecule comprising three binding sites as taught by Harris et al and add a glycosylation site as taught by Qu et al and conjugate a toxin to the site as taught by Hansen et al or add a polypeptide to the C-terminus as taught by Chaudhary et al and one site for hMN14 and one of mAb 734 because Qu et al teach adding a carbohydrate recognition site to the CH1 domain and conjugation of molecules for therapy and the CH1 domain mutants were preferred for conjugation of larger molecules for therapy and the grafting of the CH1-appended sites to other antibodies only involves simple V-region replacement (see page 144). In addition one would have used the binding site of the hMN14 and 734 antibodies because as evidenced from the specification the term "734" means an antibody that binds DTPA (see page 36) and as taught by Hansen the hMN14 binds CEA and as taught by Gautherot et al a bispecific antibody of anti-CEA and anti-DTPA was used to target tumors and treat tumors with radiolabels. Because claim 43 only recites an antibody by laboratory definition the art reads on the claim for an anti-DTPA antibody "734". It would have been obvious to label the molecules with the method of Hansen because of the advantages disclosed of not altering the antigen binding or specificity and it would have been obvious to produce a fusion protein as taught by Chaudhary et al for targeting to tumor cells and it would have been obvious to use the claimed linkers because any linker would satisfy the requirement of separating the domains.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The response filed 11/8/04 has been carefully considured but is deemed not to be persuasive. The response states that Hansen does not teach adding the site anywhere else and Chaudhary merely is directed to clone variable regions. In response to this argument, the new rejection addresses this by referring to Qu et al for adding a constant region site and conjugation and Hansen provides motivation and reasonable expectation of success to add toxins and other molecules to the added carbohydrate site. In addition, Chaudhary does not only teach cloning variable regions but efficient ways to produce fusion proteins of scFv and toxins.

Conclusion

15. No claim is allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP §

706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:00 am to 3:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

18. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 571-273-8300.

Respectfully,

Larry R. Helms Ph.D.

571-272-0832